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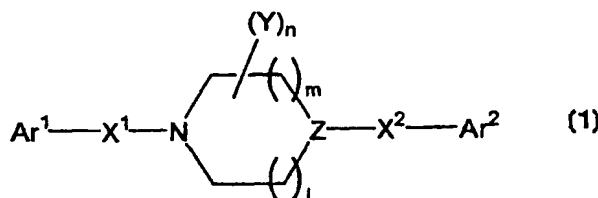
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(21) International Application Number: PCT/US99/19845		(74) Agents: FAVORITO, Carolyn et al.; Morrison & Foerster LLP, 2000 Pennsylvania Avenue, N.W., Washington, DC 20006-1888 (US).	
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(30) Priority Data: 60/098,219 28 August 1998 (28.08.98) US 60/125,343 19 March 1999 (19.03.99) US		(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, EE, GE, HU, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
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(54) Title: USE OF PIPERIDINES AND/OR PIPERAZINES AS INHIBITORS OF P38-ALPHA KINASE



(57) Abstract

The invention is directed to methods to treat conditions mediated by kinase using compounds of formula (1) and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein Z is N or CR¹, R¹ is a noninterfering substituent, each of X¹ and X² is a linker, Ar¹ and Ar² are identical or different, and represent optionally substituted C1-C20 hydrocarbyl residues wherein at least one of Ar¹ and Ar² is an optionally substituted aryl group, with the proviso that when X² is CH₂ or an isostere thereof, X¹ is CO or an isostere thereof, and Ar² is optionally substituted phenyl, Ar¹ is other than an optionally substituted indolyl, benzimidazolyl or benzotriazolyl substituent, and wherein said optionally substituted phenyl is not an optionally substituted indolyl, benzimidazolyl, or benzotriazolyl, Y is a noninterfering substituent, wherein n is an integer from 0-4, and wherein m is an integer from 0-4 and l is an integer from 0-3.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/19845

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/445 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CORP ;CHAN GEORGE W (US); BOEHM JEFFREY C (US)) 2 July 1998 (1998-07-02) cited in the application claims	1-30
X	WO 98 06715 A (RAHMAN SHIRLEY K ;SMITHKLINE BEECHAM PLC (GB); ADAMS JERRY LEROY () 19 February 1998 (1998-02-19) cited in the application claims; examples 2-4	1-30
E	WO 99 61426 A (SCIOS INC) 2 December 1999 (1999-12-02) the whole document	1-30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 May 2000

Date of mailing of the international search report

25/05/2000

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

ii. national application No.

PCT/US 99/19845

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-27
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 /19845

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to an extremely large number of possible compounds. Furthermore, the substituents are not clearly defined in the dependent claims. Claim 14, for example, mentions several cyclic moieties which cannot be considered as aryl groups. As a consequence, a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. The search had to be limited to the general inventive idea of piperidine or piperazine derivatives having P38 kinase inhibitory activity and to the compounds specifically mentioned in claim 21

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/19845

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9828292 A	02-07-1998	NONE	
WO 9806715 A	19-02-1998	EP 0922042 A	16-06-1999
WO 9961426 A	02-12-1999	AU 4092099 A	13-12-1999